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## **Serotonin syndrome after initiation of pregabalin on a stable regimen of antidepressant medication**

Jellestad, Lena ; Stocker, Lea ; Jenewein, Josef ; Boettger, Soenke

**Abstract:** Aims: Serotonin syndrome is a potentially life-threatening drug interaction caused by excess serotonin concentration in the central nervous system and/or peripheral nervous system leading to cognitive, autonomic and somatic effects ranging from barely perceptible to fatal. A number of drugs and drug interactions cause serotonin syndrome, however, the exact mechanisms often remain elusive. Presentation of Case: In the following case, serotonin syndrome was caused by the addition of pregabalin in a patient with recurrent major depressive disorder and concurrent medication with paroxetine and trazodone. Discussion: This case illustrates the risk of polypsychopharmacology leading to an increased vulnerability towards serotonin syndrome. Conclusion: Pregabalin with its serotonergic action has a liability to cause serotonin syndrome. This should be especially kept in mind in patients with polypsychopharmacology.

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## **Serotonin Syndrome after Initiation of Pregabalin on a Stable Regimen of Antidepressant Medication**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author LJ wrote the case report. Author JJ supervised the work. Author LS made corrections. Author SB managed the literature searches. All authors read and approved the final manuscript.*

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**Case Study**

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### **ABSTRACT**

**Aims:** Serotonin syndrome is a potentially life-threatening drug interaction caused by excess serotonin concentration in the central nervous system and/or peripheral nervous system leading to cognitive, autonomic and somatic effects ranging from barely perceptible to fatal. A number of drugs and drug interactions cause serotonin syndrome, however, the exact mechanisms often remain elusive.

**Presentation of Case:** In the following case, serotonin syndrome was caused by the addition of pregabalin in a patient with recurrent major depressive disorder and concurrent medication with paroxetine and trazodone.

**Discussion:** This case illustrates the risk of polypsychopharmacology leading to an increased vulnerability towards serotonin syndrome.

**Conclusion:** Pregabalin with its serotonergic action has a liability to cause serotonin syndrome. This should be especially kept in mind in patients with polypsychopharmacology.

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**Keywords:** Serotonin syndrome; pregabalin; paroxetine; trazodone.

## 1. INTRODUCTION

Serotonin syndrome (SS) is a potentially life-threatening drug interaction caused by excess serotonin in the central nervous system (CNS) and/or peripheral nervous system. As a consequence, excess serotonin causes cognitive alterations, ranging from headache to hypomania, agitation, confusion, hallucination or coma, and autonomic dysregulation with shivering, sweating, hyperthermia, tachycardia, hypertension, nausea, and diarrhea, as well as somatic, in particular, neurological alterations such as tremor, hyperreflexia and myoclonus [1]. The presenting symptomatology varies from barely perceptible, then often not acknowledged, to fatal.

Serotonin syndrome is caused by a variety of pharmacological mechanisms. Among these are the inhibition of serotonin reuptake, decreased serotonin metabolism, increased serotonin synthesis and release, and activation of serotonergic receptors [2]. Another mechanism increasing the risk for SS is the Cytochrome P450 system, in particular, the inhibition of CYP450 2D6 [3]. Clinically, SS is often caused by an overdose of single serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs), however, more frequently from drug-drug interactions of several serotonergic agents. In particular, monoamine oxidase inhibitors (MAOI) have been associated with this syndrome alongside other antidepressants such as tricyclic antidepressants (TCA), serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), bupropion, trazodone and mirtazapine, opioids with frequent reports on tramadol, CNS stimulants, 5HT<sub>1</sub>-agonists such as triptans, herbs, in particular hypericum (St. John's wort), and others such as valproate, lithium, or atypical antipsychotics.

Pathophysiologically, it was primarily suspected that the 5HT<sub>1a</sub> receptor system was involved in this syndrome, later, the 5HT<sub>2a</sub> receptor site has been identified as another contributing system, and, at last, an increase in norepinephrine levels was documented [4].

Further, various neurotransmitters have been implicated in the emergence of the SS including the N-Methyl-D-Aspartate (NMDA) - receptor, namely, antagonists at this receptor site such as

gamma-amino-butyric acid (GABA) and dopamine [5].

## 2. PRESENTATION OF CASE

Mrs. E. is a 45-year-old patient with a recurrent major depressive disorder, posttraumatic stress disorder (PTSD), opiate dependence on methadone maintenance, a combined personality disorder, and chronic medically unexplained symptoms with multilocal pain symptoms, nausea, obstipation and chronic fatigue indicating a somatization disorder.

The patient was psychiatrically hospitalized due to an exacerbation of depression and pain. She was on leave over the weekend when she experienced a change in mental status with disturbances of consciousness and cognition, as well as tremor and myoclonus of the upper and lower extremities, headache, and diaphoresis. With further aggravation of these symptoms on the following day she was urgently transferred to the University Hospital Zurich for further evaluation and management. The primary assessment revealed an inconspicuous head computed tomography scan, renal failure with decreased glomerular filtration rate (GFR: 44 ml/min), elevated inflammatory parameters (C-reactive protein 66 mg/l), elevation of ammonia 40 umol/l, upper and lower extremity clonus, resting tremor of the hands, and sedation. At the time of admission, the patient was on a stable psychotropic regimen of paroxetine 50 mg, trazodone 50 mg, bupropion XR 450 mg, paliperidone 6 mg and methadone 7.5 mg. Due to her multiple physical complaints with varying pain symptoms an antinociceptive strategy with pregabalin was initiated and gradually increased within the following weeks, reaching 750 mg on the day of admission. During the first night of hospitalization, Mrs. E. presented with a single episode of acute dyspnea and arterial hypoxemia. The chest radiography was normal, following oxygen application via face mask, administration of 125 mg methylprednisolone per os, and of 2.2 g of amoxicillin/clavulanic intravenously to cover infectious etiologies, the hypoxemia resolved, and the patient was transferred back to the regular floor. Her hemodynamic profile remained stable over the course of management.

The clinical presentation was highly suggestive of a serotonin syndrome, consequently,

trazodone and bupropion were discontinued, paroxetine was reduced to 10 mg and pregabalin to 700 mg. Within the next 48 hours, the mental disturbances and neuromuscular symptoms remitted, and the patient was transferred back to psychiatric hospital.

### 3. DISCUSSION

In this case, SS was triggered by the administration of pregabalin on top of a stable regimen of paroxetine, trazodone, bupropion, and paliperidone, all of which have been associated with SS [6-8].

Gabapentin, an analogue of pregabalin, has been shown to increase serotonin levels in the CNS [9]. Only one case report has described SS in the context of pregabalin co-administration to oxycodone preoperatively [10]. It was deduced that pregabalin, increasing the whole blood serotonin concentration in therapeutic dose ranges, in combination with oxycodone, was associated with an increased risk of developing SS. It is known that opioids beyond effects on the opioid system, also cause an increase of serotonin in the CNS through serotonin reuptake inhibition [11,12], thus, potentially causing SS [13]. In this case, the patient was on a stable regimen of methadone, which might have been an additional contributing factor for the development of SS, in addition to pregabalin at a substantial dose in combination with other serotonergic agents. Further, the patient's initial presentation with renal failure and a decrease in GFR were potential contributors to pregabalin accumulation and subsequent serotonin syndrome, since the renal pathway is the primary route of pregabalin elimination.

SS involves a spectrum of clinical findings presenting with the typical triad of SS features: 1) mental status changes 2) autonomic dysfunction and 3) neuromuscular excitability [1].

The diagnosis is made based on the clinical presentation according to the Hunter criteria [14]. These criteria state that a serotonergic agent has to be present in addition to either of the following clinical findings: Spontaneous clonus; inducible clonus and agitation; ocular clonus and agitation; tremor and hyperreflexia; hypertonia and an increased temperature ( $>38^{\circ}\text{C}$ ) and ocular or inducible clonus. In Mrs. E's case the diagnostic criteria were met with occurrence of a spontaneous clonus under serotonergic polypsychopharmacology. Another factor

predisposing to the episode of hypoventilation and hypoxemia could have been thoracic rigidity caused by SS.

In the presence of polypsychopharmacology, this case illustrates that the addition of a single agent – pregabalin - can increase the risk for serotonin syndrome. Combining serotonergic agents like antidepressants or opioids can cause excessive stimulation of the 5HT1a and 5HT2a receptors [15].

Targeting common and preventable adverse drug reactions and drug-drug interactions is crucial in ensuring patient safety and is even more challenging in susceptible sub-populations with polypsychopharmacology. Consequently, increasing research efforts have been initiated in order to enhance the knowledge on adverse drug reactions, including clinical decision support systems, databases on drug-target interactions and drug-drug interactions, as well as pharmacogenomic approaches (see [16] for a recent overview).

### 4. CONCLUSION

In summary, this is another case, illustrating the incidence of SS following the addition and titration of pregabalin on top of a stable regimen of psychotropics including serotonergic agents, in this case, paroxetine, trazodone, bupropion, paliperidone, and methadone. Although this patient had already been predisposed to SS due to her polypsychopharmacology administered prior to the development of SS, the addition of pregabalin, with its serotonergic action, triggered the onset of this syndrome. To date, pregabalin has not often been associated with SS, however, it is important, to keep its liability to cause SS in mind.

### CONSENT

All authors declare that informed consent was obtained from the patient for publication of this case report.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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